PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 16123PCT00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2005/000146	International filing date *(day/month/year)* 03.03.2005	Priority date *(day/month/year)* 03.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61B5/00 A61B18/14		
Applicant STRESSMETER A/S et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.01.2006	18.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Martelli, L Telephone No. +49 89 2399-7416

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2005/000146

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-37 as originally filed

   Claims, Numbers

   1-48 filed with telefax on 03.01.2006

   Drawings, Sheets

   1/5-5/5 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-18,43-48

because:

☒ the said international application, or the said claims Nos. 1-18,43-48 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 1-18,43-48

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19-42
	No:	Claims	
Inventive step (IS)	Yes:	Claims	19-42
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	19-42
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The independent claims 1, 14, 43, 47, 48 refer to a "method of determining the sympathetic tone" including the steps of "measuring an applied stimulation at a threshold value of the stimulation" or "measure of a nociception threshold value" or "measurement of nociception" both at neutral points and at points dependent on the sympathetic tone.
It is clear that these steps are not capable of maintaining or restoring health and physical integrity or well-being of the subject treated with that method; so the methods are not therapeutic.
They are not diagnostic methods, either, since there is, e.g., no comparison with standard values.
However, as explained in the description (page 9, lines 9-11 and 17-20 and page 15, lines 17-20), the stimulation applied to the patient necessarily causes discomfort or pain on the subject on which the method is carried out; it is also clear that the sensation of pain implies a damage to the tissue of the body.
Such an intervention is a surgical method because it involves a physical intervention on the human or animal body, no matter whether or not any therapy is achieved, since "surgery is not limited to healing treatments, being more indicative of the nature of the treatment" (Guidelines, 9.10, last sentence; see also 9.8-9).
So the claims 1, 14, 43, 47, 48 as well as the respective dependent claims 2-13 and 44-46, which contain all the surgical steps of the independent claims, are not examined according to Rule 39.1(iv) PCT.

Re Item IV

Lack of unity of invention

The application contains two groups of inventions:

Invention 1: Claims 19-30:

System including means for processing nociception threshold values to evaluate sympathetic tone.

Invention 2: Claims 31-42

System including sensor of compression exerted by pressure base on the human body.

The technical element linking the two groups of inventions is:

"system for measuring the sympathetic tone in a human being"

All the documents cited in the international search report describe such a system.

Since a technical relationship involving the special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the two groups, the requirement for unity of invention referred to in Rule 13.1 PCT is not fulfilled.

Since this International Preliminary Examination Report can be established without an additional effort compared to the invitation to restrict the claims or to pay additional fees (Rule 68.2 PCT), no such invitation is issued to the Applicant (see Rule 68.1 PCT and the Guidelines, 10.76).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.

V.1 CITED DOCUMENTS

Reference is made to the following documents, cited in the International Search Report:

D1: EP-A-0 236 513 (BARSA, JOHN E) 16 September 1987 (1987-09-16)
D2: US-B1-6 571 124 (STORM HANNE) 27 May 2003 (2003-05-27)
D3: US-A-5 673 708 (ATHANASIOU ET AL) 7 October 1997 (1997-10-07)

V.2 ARTICLE 33 PCT

V.2.1 Independent claim 19

D1, which is considered as closest prior art for claim 1, describes a system for measuring the sympathetic tone in a human being (see page 15, line 50), the system comprising:
- memory means (see page 16, lines 15-20 and 25-26) for storing a nociception calibration threshold value determined in a sympathetic-tone neutral point on the human body and for storing a nociception stimulation threshold value determined in a sympathetic-tone dependent point on the human body (D1 does not actually define the measurement point to be sympathetic-tone dependent or not; however, the memory means of are D1 are suitable for storing the measured values).

The subject-matter of claim 19 differs from the known system by:

- an electronic circuit programmed to data process the nociception calibration threshold value and the nociception stimulation threshold value so as to obtain the measurement of the sympathetic tone.

So claim 19 is new (Article 33(2) PCT).

D1 does not describe such an electronic circuit. Neither D1 nor the available prior art deals with the problem of evaluating sympathetic-tone dependent points and sympathetic-tone dependent points. For this reason claim 19 is considered as involving an inventive step (Article 33(3) PCT).

V.2.2 Independent claim 31

D3 is considered closest prior art for claim 31 and discloses a system (110, see column 10, line 32) for measuring the sympathetic tone in a human being (although the measurement of sympathetic tone is not mentioned in D3, the system it describes is suitable for this use), the system including:
- a pressure base (122, see column 10, lines 46-47 and column 13, lines 41-42) with a contact face adapted to exert an outer compressive force on the human body;
- a sensor (124, see column 13, lines 61-64) for measuring the compressive force

exerted by the pressure base on the body;
- an electronic circuit (190, see column 14, lines 11-13 and 49) adapted to:
  - store a first measured compressive force (see column 14, lines 46, 47, 50) and a second measured compressive force (see column 14, lines 52-53), respectively, and to
  - calculate a read-out value (see column 14, lines 46-53) as an expression of the ratio between the first measured compressive force and the second measured compressive force

and wherein the system includes
- a read-out unit (see column 14, line 58) for displaying the read-out value.

The subject-matter of claim 31 differs from the known system of D3 by:

- the contact face of the pressure base being resilient.

According to D3, the contact face is rigid (see column 13, lines 13-16); in fact, in order to correct measure the cartilage displacement, if the contact face of the pressure base were resilient, the measured displacement would include an incorrect quantity due to the resilient deformation of the contact face as a function of the applied force.

The problem to be solved by this feature is considered as to adapt the system of D1 (which is designed to test cartilage displacement on applying a force) to better measure the sympathetic tone so that measurement can be carried out on uneven surfaces and provides a uniform pressure.

Since the prior art documents do not deal with this problem, claim 31 is considered as involving an inventive step.

V.2.3 Dependent claims

The claims 20-30 and 32-42 are dependent on claims 19 and 31, respectively, and as such also meet the requirements of the PCT with respect to novelty and inventive step.

16123PCT00

INTERNATIONAL PATENT APPLICATION NO. PCT/DK2005/000146

NEW CLAIMS UNDER ART. 34 PCT, FAIR VERSION

1. Method of determining the sympathetic tone including the steps of: measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value in one or more sympathetic tone-dependent points.

2. Method according to claim 1, wherein the applied stimulation is provided by means of an applied mechanical stimulation.

3. Method according to claim 2, wherein the applied mechanical stimulation is provided by means of an applied compressive force.

4. Method according to claim 1, wherein the applied stimulation is provided by means of an applied thermal stimulation.

5. Method according to claim 4, wherein the applied thermal stimulation is provided by means of an applied heat or cold source.

6. Method according to claim 1, wherein the applied stimulation is provided by means of an applied radiation.

7. Method according to claim 6, wherein the applied radiation is provided by means of an applied infrared, visible and/or ultraviolet light or combined spectra thereof.

8. Method according to claim 1, wherein the applied stimulation is provided by means of an applied chemical stimulation.

9. Method according to claim 8, wherein the applied chemical stimulation is provided by means of an applied organic or inorganic compound.

10. Method according to any one of the preceding claims, wherein the determination is performed by means of a system for measuring the applied stimulation.

11. Method according to any one of the preceding claims, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-

neutral points is carried out anteriorly on the upper side of the clavicle and/or posteriorly on the spinal column corresponding to TH 10-11.

12. Method according to any one of the preceding claims, wherein the measuring of an applied stimulation at a threshold value of the stimulation is carried out in one or more sympathetic tone-dependent points at one or more locations on the skin which innervationally correspond to the nerve supply to the heart of the sympathetic nervous system.

13. Method according to any one of the preceding claims, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-dependent points is carried out in one or more of the points: C.V. 17 in the middle of the sternum and/or St 18 between two ribs below the nipple and/or Per 1 between the nipple and the anterior axillary fold and/or on the spinal column corresponding to TH 3-6, where the most sore point of the said points are chosen.

14. Method of quantitative determination of sympathetic tone in a human, said method including:

a) storage of a calibration threshold value and a stimulation threshold value, the calibration threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-neutral point on a human body and the stimulation threshold value being a quantitative measure of a nociception threshold value in a sympathetic tone-dependent point on the human body, and subsequently;

b) calculation of an indication value of sympathetic tone by comparing the stimulation threshold value with the calibration threshold value, whereby the indication value of sympathetic tone is a measure of the sympathetic tone in the human being.

15. Method according to claim 14, wherein the calibration threshold value and the stimulation threshold value are measured substantially simultaneously.

16. Method according to claim 14 or 15, wherein nociception is induced by means of exposure to compressive force, heat, cold, radiation, chemical stimulation or combinations thereof.

17. Method according to any one of the claims 14-16, wherein a significantly lower nociception threshold value being obtained in a sympathetic tone-dependent point than in a sympathetic tone-neutral point indicates that a person has increased sympathetic tone.

18. Method according to any one or the claims 14-17, wherein the indication value of the sympathetic tone is compared to at least one previously determined indication value of sympathetic tone, said previous value indicating sympathetic tone at an earlier point in time and/or a result of said value.

19. System for measurement of the sympathetic tone in a human being, said system including:

a) Memory means for storing a nociception calibration threshold value determined in a sympathetic tone-neutral point on the human body and for storing a nociception stimulation threshold value determined in a sympathetic tone-dependent point on the human body;

b) An electronic circuit programmed to data process the nociception calibration threshold value and the nociception stimulation threshold value so as to obtain the measurement of the sympathetic tone.

20. System according to claim 19 and which further includes user-operated means for applying a discomfort-evoking stimulus to the surface of the human body and user-operated storage means adapted to:

a) store the nociception calibration threshold value resulting from a first user operation;

b) store the nociception stimulation threshold value resulting from a second user operation.

21. System according to claim 20, wherein the means for applying a discomfort-exvoking stimulus is contained in a first unit and where the said electronic circuit is contained in a second unit.

22. System according to claim 21, wherein the first and the second units are adapted to allow wireless communication between the first unit and the second units.

23. System according to claim 20, wherein the means for applying a discomfort-evoking stimulus and the said electronic circuit are integrated in one and the same apparatus.

24. System according to any one of the claims 20-23, wherein the means for applying a discomfort-evoking stimulation are adapted to apply a stimulus which is gradually increased, the storage means being adapted to store a stimulation level at a moment in time corresponding to the first and the second user operation, respectively.

25. System according to claim 24, wherein the applied discomfort-evoking stimulus includes an exposure to compressive force, heat, cold, radiation, chemical stimulation or combinations thereof.

26. System according to claim 25, wherein the compressive force is applied by means of a pressure base (5) or a clamp.

27. System according to any of the claims 19-26, wherein the applied discomfort-evoking stimulus is discontinued at the time of the first or second user operation.

28. System according to claim 27, wherein the contact face (6) of the pressure base (5) is resilient.

29. System according to claim 28, wherein the pressure base (5) contains a liquid, a gel and optionally gas-filled bubbles.

30. System according to any one of the claims 26-29, wherein the area of the contact face (6) is less than 4 cm^2, preferably between 1 and 2 cm^2.

31. System (4) for measuring the sympathetic tone in a human being, said system including a pressure base (5) with a contact face (6) adapted to exert an outer compressive force on the human body, a sensor (7) for measuring the compressive force exerted by the pressure base (5) on the body, an electronic circuit adapted to store a first measured compressive force and a second measured compressive force, respectively, and to calculate a read-out value as an expression of the ratio between the first measured compressive force and the second measured compressive force and wherein the system includes a read-out unit (8) for displaying the read-out value, wherein the contact face (6) of the pressure base (5) is resilient.

32. System according to claim 31, wherein the pressure base (5) and the sensor (7) are integrated in a first unit and wherein the said electronic circuit is integrated in a second unit.

33. System according to claim 32, wherein the first and the second units are adapted such to allow wireless communication between the first unit and the second unit.

34. System according to claim 31, wherein the pressure base (5), the sensor (7) and the said electronic circuit are integrated in one and the same apparatus.

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35. System according to any one of claims 31-34, wherein the pressure base (5) contains a liquid, a gel and optionally gas-filled bubbles.

36. System according to any one of the claims 31-35, wherein the area of the contact face (6) is less than 4 cm^2, preferably between 1 and 2 cm^2.

37. System according to one of the claims 31-36, wherein the sensor (7) is a piezoresistive force sensor.

38. System according to one of the claims 31-37, said system being hand-held and supplied with power by one or more batteries.

39. System according to one of the claims 31-38, wherein the read-out unit is an electronic display (8).

40. System according to one of the claims 31-39, wherein the electronic circuit is adapted to determine the read-out value as one of a number, eg. four, discrete read-out values (0, 1, 2, 3), the ratio between the first measured value and the second measured value being allocated a discrete read-out value (0, 1, 3, 4) displayed on the read-out unit (8).

41. System according to claim 40, wherein the discrete read-out value (0, 1, 2, 3) is non-proportional to the ratio between the first measured value and the second measured value.

42. System according to one of the claims 31-41, wherein the electronic circuit is adapted to calculate the first measured value as an average of a number of measured values and calculate the second measured value as an average of a number of measured values.

43. Use of a system for applying and measuring a stimulation for determining the sympathetic tone including the steps of: measuring an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points and measuring an applied stimulation at the same threshold value of the stimulation in one or more sympathetic tone-dependent points.

44. Use according to claim 43, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-neutral points is carried out on the upper side of the clavicle and/or on the spinal column corresponding to TH 10-11.

45. Use according to claim 43 or 44, wherein the measuring of an applied stimulation at a threshold value of the stimulation is carried out at one or more points on the skin, said points innervationally corresponding to the nerve supply to the heart from the sympathetic nervous system.

46. Use according to any one of the claims 43-45, wherein the measuring of an applied stimulation at a threshold value of the stimulation in one or more sympathetic tone-dependent points is carried out in one or more of the points: C.V. 17 in the middle of the sternum and/or St 18 between two ribs below the nipple and/or Per 1 between the nipple and the anterior requirement and/or on the spinal column corresponding to TH 3-6, where the most sore point of the said points is chosen.

47. Use of measurement of nociception in sympathetic tone-neutral points and in sympathetic tone-dependent points for determining the sympathetic tone.

48. Use of measurement of nociception in a conscious human being for determining sympathetic tone.